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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/313,292	05/13/1999	LEWIS T. WILLIAMS	1487.002	3706

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EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 03/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/313,292	WILLIAMS ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *123-130* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *123-130* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Technology Center would have requested that the Deputy Commissioner for Patent Examination Policy approve a request for rehearing by the Board of Patent Appeals and Interferences of the decision of 29 September 2005, but for the reopening of prosecution to treat the enablement issue. In the event that the written description issue remains after the further prosecution to further treat the enablement issue is concluded, applicant is placed on notice that the Technology Center may resurrect the written description issue and request that the Deputy Commissioner for Patent Examination Policy approve a request for rehearing by the Board of Patent Appeals and Interferences of the decision of 29 September 2005.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 123-130 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or

absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must use the claimed polynucleotides in a diagnostic assay as discussed in the specification on pages 59-60 to determine if clinical samples from a patient comprise breast cancer cells to guide therapeutic choices for the patient. This method of use requires a correlation between expression level of mRNA encoded by the claimed polynucleotides and breast cancer. For the reasons discussed below there would be an unpredictable amount of experimentation required to use the claimed polynucleotides.

b) The specification presents guidance on pages 59-62 to use polynucleotides comprising the sequence of SEQ ID NO:972 in a breast cancer diagnostic assay by determining the level of mRNA in a patient clinical sample that is encoded by SEQ ID NO:972. The specification shows that partial cDNA libraries from the human breast tumor cell line MDA-MB-231 (described in the specification on pages 57-59 as high metastatic potential cells) contain about 6 times as many library members comprising SEQ ID NO:972 as do partial cDNA libraries from the human breast tumor cell line MCF-7 (described in the specification on pages 57-59 as low metastatic potential cells).

c) The specification does not present working examples of using polynucleotides comprising SEQ ID NO:972 in a clinical diagnostic assay.

d) The nature of the invention, polynucleotides useful for cancer diagnostic assays, is complex.

e) Brinkley et al. shows in Table 1 on page 3122 that the human breast cancer cell line MDA-MB-331 has extensive arrays of microtubules ("Type 1") and is tumorigenic in nude mice. However Brinkley et al. also shows that other tumorigenic human breast cancer cell lines differ from MDA-MB-331 in the morphology of their cytoskeleton, and Brinkley et al. conclude on pages 3122-3123 that the cytoskeletal structure of cell lines is an unreliable marker for their malignancy. Chandrasekaran et al. quantified the glycosaminoglycan content of a normal human breast cell line, and two human breast cancer cell lines, MCF-7 and MDA-MB-231. Chandrasekaran et al. shows on pages 871-873 that each cell line produces a different spectrum of glycosaminoglycans and that their analysis does not show a correlation between glycosaminoglycan content and whether the cell is isolated from tumor or normal tissue. Clarke et al. shows that breast cancer cells tend to progress from nonmetastatic estrogen dependent stages to metastatic estrogen independent stages. Clarke et al. shows that the MCF-7 cell line is estrogen dependent for growth in culture, but that subclones of the MCF-7 cell line could be isolated that are estrogen independent for growth in culture (see Table 1, page 3650). However Table 2 show that all cell lines examined remain estrogen dependent for growth when implanted into ovariectomized nude mice. The parental MCF-7 and BSK-2 and BSK-3 subclones are not invasive, but the MIII subclone is invasive (see Figure 4). The prior art teaches that the correlation between cancer cell lines and primary tumor tissue relationships are highly unpredictable. Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teaches that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in an artificial environment. Dermer *et al.* states that "the petri dish cancer is really a poor representation of malignancy, with

characteristics profoundly different from the human disease." Further, Chabert *et al.* (Int. J. Cancer: 53, 837-842 (1993)) compares PARP gene expression, enzymatic activity and quantities in 3 animal tumor cell lines in culture verses those transplanted into a compatible host, and found that, for "a given tumor cell line, marked differences exist in poly(ADPR)P gene expression and enzymatic activity between cultured cells and cells obtained from solid or ascitic tumors. Indeed, poly(ADPR)P gene expression, endogenous activity and amount are higher in exponentially growing cells than in *in vivo* tumors (p. 837, see also Fig. 1)." Chabert *et al.* further suggests that such discrepancies in enzymatic activity between cell culture and in vivo growth conditions exist because of differences in proliferation rates and/or environmental conditions (p. 841). Odum *et al.* (Toxicology in Vitro 12 (1998) 273-278) also teaches that the two breast cancer cell lines used by the applicants to select cDNA clones that correlate with metastatic breast cancer disease respond to xenobiotic estrogens in an unpredictable manner. Though Odum *et al.* does not screen for gene expression in particular, the disclosure underscores the unpredictable behavior breast cancer cell lines versus primary tumor tissue.

The prior art summarized above shows that different cell lines derived from breast tumors have divergent properties. The prior art does not show cell line phenotypes or genetic markers that consistently distinguish between non-metastatic and metastatic tumors in patient clinical samples. The prior art does not show that expression of SEQ ID NO: 972 correlates with non-metastatic or metastatic patient clinical samples.

f) The skill of those in the art of cancer biology is high.

g) The prior art does not show the likelihood of discovering genetic markers that correlate with metastatic potential of human breast clinical isolates.

h) The claims are broad in that they are drawn to a polynucleotide that can be used to predict metastatic potential of human breast isolates.

The skilled practitioner would first turn to the instant specification for guidance to use the claimed polynucleotides. The specification shows that SEQ ID NO: 972 is 6 times more likely to be isolated from the MDA-MB-231 cell line than from the MCF-7 cell line. However the specification does not establish that differences between gene expression levels in MDA-MB-231 cells and MCF-7 cells has any correlation with metastatic potential in human breast samples. As such the skilled practitioner would turn to the prior art to validate the relevance of expression levels of SEQ ID NO: 972 for diagnosis of metastatic potential in human breast samples. However the prior art shows that different cell lines derived from human breast cancer samples have divergent properties, and that the prior art does not show a strong correlation between a measured phenotype of a breast cancer cell line and the metastatic potential of the tissue from which the cell line was derived. Finally said practitioner would turn to trial and error experimentation to determine if polynucleotides comprising SEQ ID NO: 972 could be used in breast cancer metastatic potential assays or for any other purpose. Such represents undue experimentation.

Conclusion

4. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of

document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center at (800) 786-9199.Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is 571 272-0714. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, PhD. can be reached on 571 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

6 February 2006

John S. Brusca
Primary Examiner
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